SYNTHESES AND APPLICATIONS OF NOVEL *β*-AMINO ACIDS

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ABBREVIATIONS

ACPC	aminocyclopentanecarboxylic acid
AIBN	azobis(isobutyronitrile)
AIDS	acquired immune deficiency syndrome
atm.	atmosphere
Boc	*tert*-butyloxycarbonyl
CAL-B	*Candida antarctica* lipase B
CSI	chlorosulfonyl isocyanate
DABCO	1,4-diazabicyclo[2,2,2]octane
DBU	1,8-diazabicycloundec-7-ene
DHP	dihydropyridine
DMAP	4-dimethylaminopyridine
DNA	desoxyribonucleic acid
HIV	human immunodeficiency virus
MCR	multicomponent reaction
MW	microwave
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser enhancement spectroscopy
TBS	*t*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
p-TSA	*para*-toluenesulfonamide
U-4CC	Ugi four-component condensation
U-4CR	Ugi four-component reaction
U-4C-3CR	Ugi four-centre three-component reaction
U-5C-4CR	Ugi five-centre four-component reaction

1. INTRODUCTION AND AIMS

In the past decade, the number of investigations on *β*-amino acids, in both racemic and optically active form, has risen exponentially in consequence of their increasing chemical and biological importance. *β*-Amino acids and their derivatives possess noteworthy pharmacological effects; for example, the first natural alicyclic *β*-amino acid, (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid (ACPC; cispentacin), isolated from *Bacillus cereus*[1, 2] and *Streptomyces setonii*[3, 4] in 1989, 2-amino-3-cyclohexenecarboxylic acid[5, 6] (originally designed as a pyridoxal phosphate suicide inhibitor) and (1*R*,2*S*)-2-amino-4-methylenecyclopentanecarboxylic acid[7, 8] (Icofungipen; clinical studies are currently in progress) display antifungal activity. Icofungipen, a *β*-amino acid, perturbs the biosynthesis of an essential protein in *Candida albicans*.[9, 10]

β-Amino acids can also be used as building blocks of modified analogues of pharmacologically active peptides.[11-13] By insertion of an alicyclic *β*-amino acid in place of an *α*-amino acid in a naturally-occurring pharmacologically active peptide, the activity or the effect can be modified. By means of such an exchange, the stabilities of these amended peptides are increased, since the *β*-peptides are resistant to enzymatic degradation.[14] *β*-Amino acids and their foldameric oligomers are now at the focus of research interest.[15-19]

Their derivatives, such as amino esters, amides and 1,3-amino alcohols may serve as excellent building blocks for the synthesis of a wide range of saturated heterocycles.[20-22]

As the great importance of *β*-amino acids and the previous results have been surveyed in several articles, reviews,[20-23] the literature overview in this thesis focuses on chemical transformations in aqueous medium. Quite recently chemists have begun investigations of the possibility of using water as solvent for organic reactions sometimes with surprising findings.

The observations reported from the laboratories of Breslow[24-26] and Grieco[27, 28] on the positive effects of water on the rates and selectivities of Diels-Alder reactions are often regarded as the “Big Bang” in aqueous synthesis that induced extensive interest in this possibility. Significant progress has subsequently been made in the field of organic chemistry in aqueous media, and new results are continuously supplementing the list of organic transformations that can be performed efficiently in water as solvent.

Combinatorial chemistry is currently a rejuvenated branch of organic chemistry and serves as a highly efficient tool in drug discovery, large number of compounds being created

within a short time. In connection with combinatorial chemistry, the isocyanide-based multicomponent condensation reactions (MCRs), such as the Ugi four-component reaction (U-4CR) have become popular and several reviews have been published on this subject.[29-32]

The research work relating to this thesis covered three topics connected with *β*-amino acids enantioselective syntheses of chiral auxiliaries and building blocks based on natural monoterpene sources; hydroxy group functionalization of alicyclic *β*-amino acids; and the application of combinatorial chemistry in aqueous medium to produce *β*-lactam libraries.

Our primary aim was to prepare *β*-amino acid derivatives which may be utilized as chiral auxiliaries and catalysts in enantioselective syntheses, or as chiral building blocks in the asymmetric syntheses of potential pharmacons, *β*-amino acid oligomers and modified analogues of natural peptides. We set out to achieve the syntheses and transformations (*e.g.* cyclization) of homochiral *β*-amino acid derivatives prepared from (+)-3-carene, a commercially available homochiral source [I].

A second aim was to study the iodocyclization of unsaturated *β*-amino acid derivatives in order to obtain saturated analogues of the first alicyclic hydroxy-*β*-amino acid oryzoxymycin [II], which was extracted from *Streptomyces* species by Hashimoto *et al.*[33, 34] and demonstrated to exhibit moderate activity against *Xanthomonas oryzae*.[35]

A third aim was to investigate the effect of water as solvent in the Ugi four-centre three-component reaction (U-4C-3CR) and compare the results with those of reactions in organic solvents. Through the application of alicyclic *β*-amino acids as building blocks, bi- and tricyclic *β*-lactam libraries were generated in aqueous medium [III].

Since the chemistry and pharmacology of cyclic *β*-amino acids have been widely reviewed in an earlier thesis, in the present literature survey we focus on the use of water as solvent in different organic syntheses.

The publications on which this thesis is based are given in square brackets, while other literature references are given as superscripts.

2. LITERATURE

2.1. Advantages of using water as solvent

There are a number of benefits of replacing organic solvents with water for *e.g.* it is non-toxic, readily available at low cost, non-flammable and environmentally benign, these advantages not being gained at the expense of synthetic efficiency. Hydrophobic effects, when an aqueous phase is used can either accelerate reactions or enhance their selectivities without reference to the solubility of the reactants. Additionally, the low solubility of gaseous oxygen in water can facilitate air-sensitive transition-metal catalysis in the open air. Labour-intensive experimental procedures can be simplified since organic products can be isolated, water-soluble reagents recycled and catalysis performed through phase separation. Water-soluble compounds can be applied directly without any tedious derivatization, and an aqueous medium allows the elimination of laborious protection-deprotection processes for certain acidic hydrogen-containing functional groups.

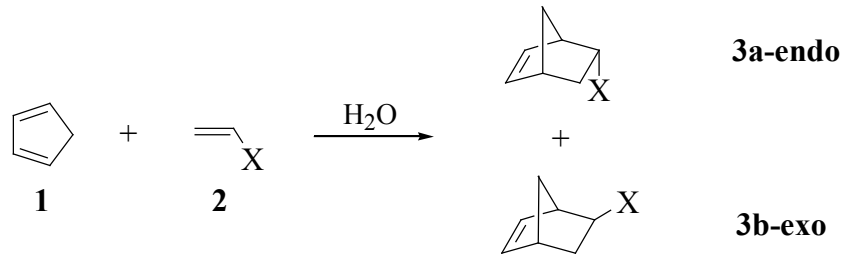
Water has a high specific heat capacity, which permits the more facile control of exothermic reactions, and has a network of hydrogen bonds which can influence the reactivity of substrates.[36] Other interesting characteristics of water are that additives such as salts can be used, inducing salt-in or salt-out effects, surfactants and cyclodextrins can be added, the pH can be varied, and cosolvents or biphasic reaction systems can be utilized.

2.2. Condensation reactions in aqueous medium

Since several reviews of investigations in aqueous medium have covered almost all kinds of organic reactions,[37-40] focus here on current results of condensation reactions, highlighting various benefits of water as solvent.

For many hundreds of years, water was the only solvent accessible to chemists to perform syntheses. With the introduction of organic solvents, a new period in chemistry was born. Chemists have recently begun to reinvestigate the possibility of applying water as a solvent for organic reactions. Diels-Alder reactions in aqueous media were reported in the 1930s,[41] and water was later found to enhance the rates and selectivities of the reaction between cyclopentadiene **1** and different dienophiles **2** (Scheme 1).[42] This unusual

accelerating effect of water was explained in terms of enforced hydrophobic interactions and hydrogen-bonding interactions. With cyclopentadiene as solvent the *endo*:*exo* (**3a**:**3b**) ratio was approximately 4:1, but this was increased to 21:1 in water (Table 1).



Scheme 1

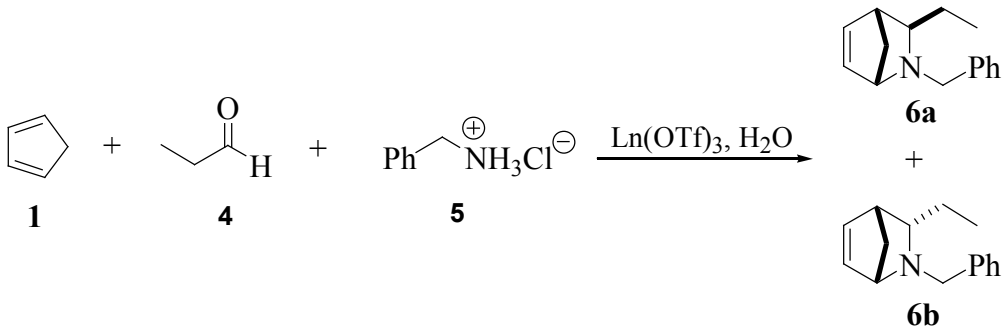
Table 1. *Endo*:*exo* product ratios in Diels-Alder reactions of cyclopentadiene and different dienophiles in organic media and in water

Medium	Formal concentration of diene and dienophile (M)	Dienophile	*Endo*:*exo* ratio
cyclopentadiene	excess diene[c]	butenone	3.85
		methyl acrylate	2.9
		dimethyl maleate	2.8
		methyl methacrylate	0.43
H_2O	**0.15**	**butenone**	**21.4**[a]
		methyl acrylate	**9.3**
		dimethyl maleate	**13.7**[b]
		methyl methacrylate	**1.4**

a. Yield > 80% after 3 h. b. Yield 75% after 26 h. c. Diene was used as solvent

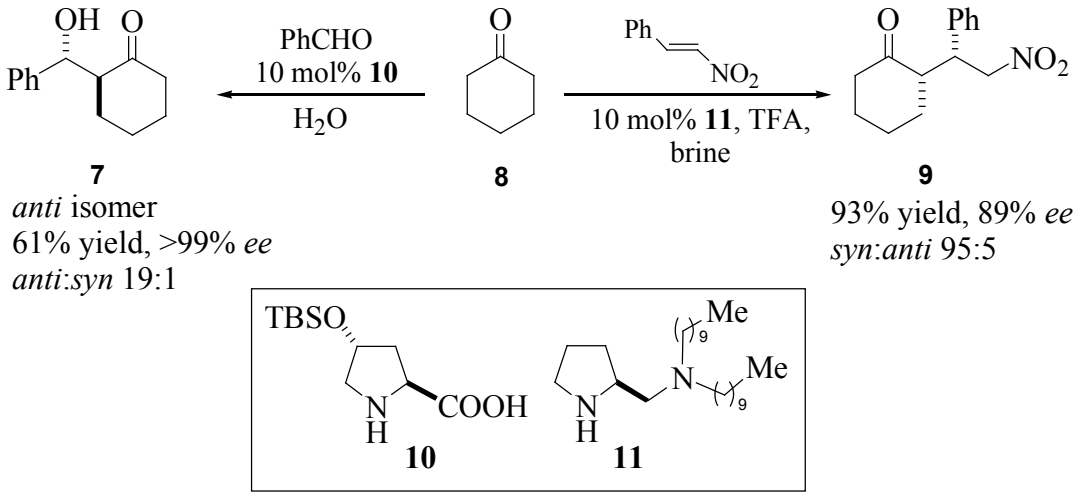
Following this report, numerous other Diels-Alder reactions were investigated, where the water solubility of the diene or the dienophile was increased by the introduction of acidic[43] or other hydrophilic[44] moieties. Other additives, such as Lewis acids can be applied in aqueous reactions, in particular as catalysts in Diels-Alder reactions. In recent years, various water-tolerant Lewis acids have been developed such as $[Cu(NO_3)_2 \cdot 3H_2O]$, the Zn^{2+}-, Ni^{2+}- or Co^{2+}-containing analogues,[45] lanthanide triflates $(Ln(OTf)_3)$[46] and $InCl_3$ derivatives.[47] In a

three-component hetero Diels-Alder reaction, when no $Ln(OTf)_3$ was added, the product **6** (**6a** + **6b**) was isolated in a yield of only 4%; whereas the presence of this catalyst enhanced the yield of **6** to 64% (Scheme 2).[L/13]



Scheme 2

In consequence of the increasing interest in organocatalysis, a number of asymmetric organocatalytic processes have been reported in aqueous medium.[49] These methods included the application of proline-based catalysts in asymmetric aldol reactions (with the application of **10**) with high stereo- and enantioselectivities (>99% *ee*)[50] or the Michael additions of ketones and aldehydes with *β*-nitrostyrene (with **11**) in brine (Scheme 3).[51]

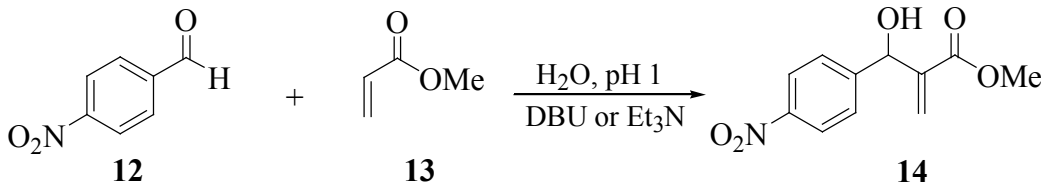


Scheme 3

Traditionally, organometallic reactions have been performed under anhydrous conditions in an inert atmosphere. In recent years, however, organometallic-catalysed transformations, such as cyclopropanations, carbonylations and alkylations, have been

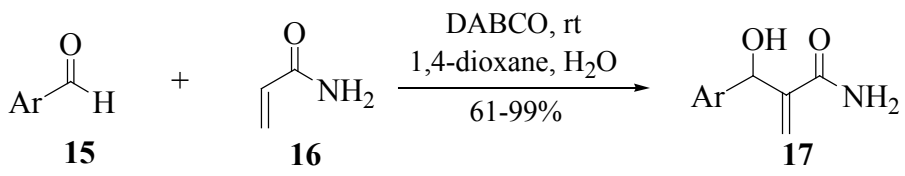
described in aqueous medium by different authors.[52-54] Many water-soluble catalysts (*e.g.* water-soluble Ru-, Rh-, Pd- and Au-based compounds) have been utilized in a broad range of transformations.

Since the first report of the Baylis-Hillman reaction in the 1970s, this C–C bond-forming reaction has been widely used in organic synthesis.[55-57] The reaction is typically catalysed by tertiary amines such as 1,4-diazabicyclo[2,2,2]octane (DABCO), 1,8-diazabicycloundec-7-ene (DBU) and quinuclidines.[58] More recently the reaction was reported to be accelerated in the presence of water.[59, 60] Caumul and Hailes investigated the use of aqueous acidic conditions for the Baylis-Hillman reaction in the presence of tertiary amines.[61] 2-Nitrobenzaldehyde **12** and methyl acrylate **13** were used as substrates at 0 ºC following by pH adjustment (pH 1) with concentrated HCl. Further addition of Et_3N resulted in 74% yield, and compound **14** was formed in 52% yield with DBU (Scheme 4). The reaction was then performed with benzaldehyde over a pH range (at 0 or 25 ºC) to confirm the effect of the acidity on the reaction. It was noteworthy that the yield of the reaction increased with decreasing pH.



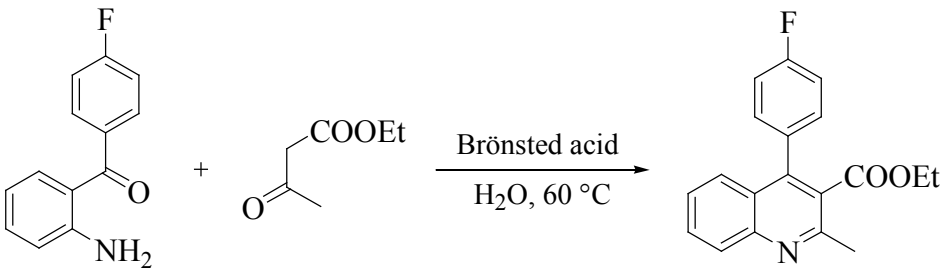
Scheme 4

In another example of the Baylis-Hillman reaction, aldehydes **15** were reacted with acrylamide **16** in the presence of a basic catalyst, DABCO, in a 1:1 mixture of dioxane and water at ambient temperature, resulting in the corresponding 3-hydroxy-2-methylenepropionamides **17** in 61-99% yield (Scheme 5).[62]



Scheme 5

The quinoline nucleus occurs in several natural compounds (*e.g.* cinchona alkaloids) and pharmacologically active substances displaying a broad range of biological activity, such as anti-asthmatic, antibacterial, anti-inflammatory and antihypertensive properties. In addition to the medical applications, quinolines have been employed in the study of bioorganic and bioorganometallic processes. Numerous well-known procedures have been utilized to synthetize them, *e.g.* the Skraup, Doebner-von Miller, Friedländer and Combes reactions, but most of these methods need a labour-intensive work-up, a long reaction time and application of a harmful organic solvent, and low yields are still observed. The starting materials for the Friedländer synthesis are *o*-aminoaryl aldehydes or ketones and a ketone possessing an *α*-methylene group. After an initial amino-ketone condensation, the intermediate undergoes base- or acid-catalysed cyclocondensation to produce a quinoline derivative. Wang *et al.* first described the aqueous Friedländer synthesis of quinolines. The condensation between benzophenone derivative **18** and ethyl acetoacetate **19** was completed within 0.5-6 h furnishing quinoline derivative **20** in 85-96% yield (Scheme 6).[63]

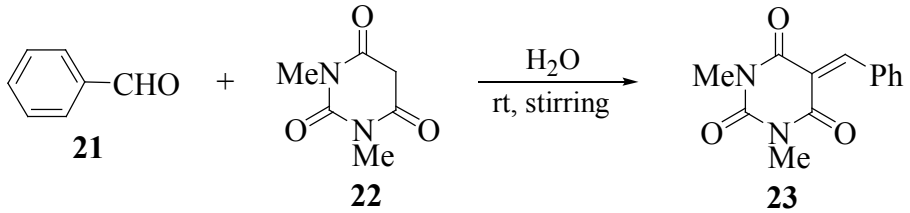


18 **19** **20**

Scheme 6

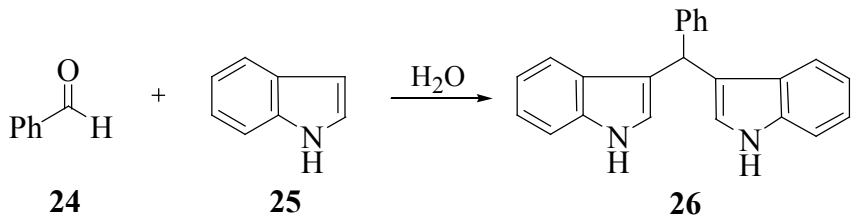
The Knoevenagel condensation of aldehydes with active methylene compounds is an important and widely-employed method for C-C bond formation in organic synthesis,[64] with numerous applications in the synthesis of chemicals,[65] in hetero Diels-Alder reactions[66] and in the synthesis of carbocyclic and heterocyclic[67] compounds of biological significance. In an organic solvent, it is necessary to apply different catalysts, *e.g.* amines, NH_3 or NaOEt. The experiments of Deb and Bhuyan simplified this procedure, the condensations of aromatic or heteroaromatic aldehydes and active methylenes in water without any catalyst proceeding within minutes (3-60 min) in excellent yields (80-98%) at room temperature. As an example,

the product **23** was isolated by simple filtration after stirring for 5 min (98% yield) (Scheme 7).[68]



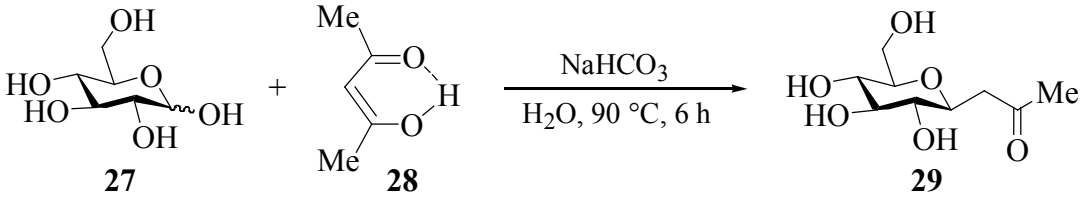
Scheme 7

Bis(indolyl)methanes feature widely among bioactive metabolites of terrestrial and marine origin, and appreciable effort has therefore been devoted to the synthesis of these molecules. Deb and Bhuyan also investigated the condensation of different aldehydes and indoles to synthetize bis(indolyl)methanes. Scheme 8 illustrates the reaction starting from benzaldehyde **24** and indole **25**.[69] While the reaction was complete in 2.5-20 h in MeOH, water as solvent decreased the reaction time to 1-5 h at room temperature, without significant change in the yield (55-96% in water).



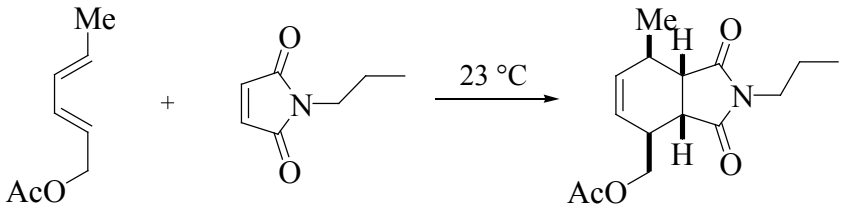
Scheme 8

One of the most important benefits of using water as solvent in organic reactions is that water-soluble compounds bearing polyhydroxy functional groups can be used directly without labour-intensive protection-deprotection processes. This property can be utilized particularly in carbohydrate chemistry. In organic solvents, the *β*-C-glycosidic ketone **29** was synthetized from protected D-glucose in several steps, in low overall yield. In sharp contrast, starting from D-glucose **27** and pentane-2,4-dione **28** in aqueous medium, **29** was obtained in one step in almost quantitive yield (Scheme 9).[70]



Scheme 9

One major concern regarding the use of water has always been the solubility of the reacting substrates. Narayan *et al.* focused on various organic reactions in the presence of water when the organic substrates are insoluble in water. The reactions proceeded efficiently and a spectacular rate acceleration was observed. They described various reactions including cycloadditions (*e.g.* Scheme 10), an ene reaction, Claisen rearrangement and nucleophilic ring opening of an epoxide both in organic solvents and in water.[71]



Scheme 10

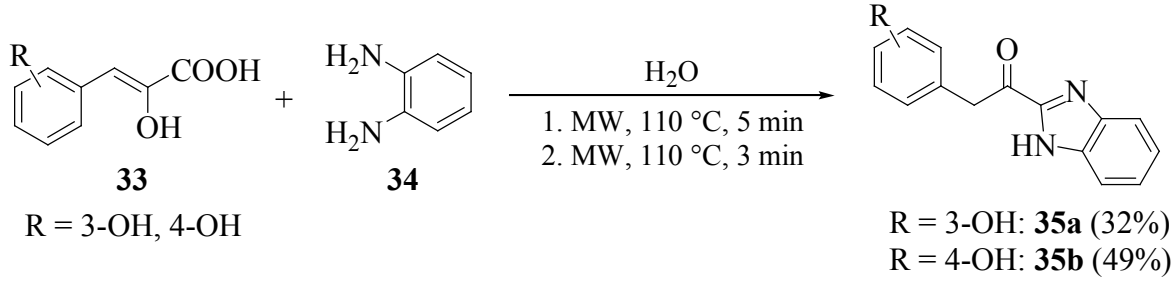
Table 2 compares the results obtained with different organic solvents. Either in organic solvents or neat, product **32** was obtained in 43-82% yield in 10-144 h, whereas in the presence of water the reaction was complete in 8 h, resulting in **32** in 81% yield.

Table 2. Cycloaddition reactions (Scheme 10) in organic solvents or in the presence of water

Solvent	Time (h)	Yield (%)
toluene	144	79
MeCN	>144	43
MeOH	48	82
neat	10	82
H_2O	**8**	**81**

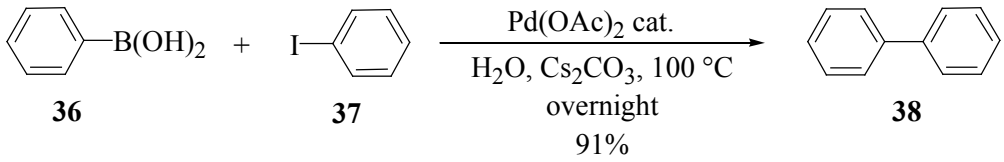
A large number of recent publications have reported the combination of an aqueous medium with the use of microwave (MW) irradiation as an efficient heating method.[72] In recent years, the combination of the two prominent green chemistry principles, MW irradiation and water, has become very popular. Since the first reports of the application of MW heating to accelerate organic chemical transformations by Gedye *et al.* and Giguere *et al.* in 1986,[73, 74] more than 3500 articles have been published on MW-assisted organic synthesis. In the present literature survey, merely a few interesting examples can be highlighted.

The synthesis of potential HIV-1 integrase inhibitor benzimidazoles **35a,b** was achieved by Ferro *et al.* by condensation of *α*-hydroxycinnamic acids **33** and 1,2-phenylenediamine **34** in aqueous medium (Scheme 11).[75] Two irradiation cycles of 5 and 3 min at 110 °C were applied as the method of generation; the heterocycles were obtained in moderate yields (32-49%). As compared with the conventional heating at 120 °C (2 h), the reaction time was significantly shorter under MW conditions (8 min).



Scheme 11

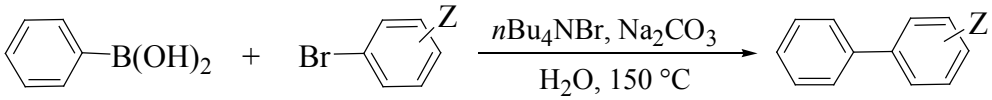
The Suzuki reaction (Pd-catalysed cross-coupling of aryl halides with boronic acids) is one of the most often used C-C cross-coupling methods and has often been carried out in an organic/aqueous mixed solvent.[76, 77] A large number of publications have reported successful Suzuki coupling by using a mixed solvent or water.[38] A few years ago, Venkatraman *et al.* studied Suzuki reactions in an oxidative atmosphere in water.[78, 79] They found that cross-coupling proceeded smoothly in water under an atmosphere of air with either $Pd(OAc)_2$ or Pd/C as catalyst (Scheme 12). Suzuki reactions involving the use of air and water were investigated in a variety of systems.[80, 81]



36 **37** **38**

Scheme 12

The use of MW heating is a convenient method with which to facilitate Suzuki reactions in water.[82-84] Recently Leadbeater and Marco found that the Suzuki reaction can be achieved in water as solvent at 150 ºC without addition of any Pd source (Scheme 13).[85, 86]



36 **39** **40**

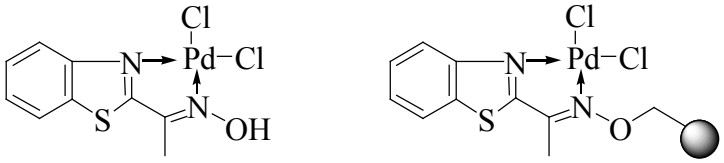
Z = Me, OMe, Cl, NH_2, NO_2, CHO, COMe, COOH, COOR

Scheme 13

Various aryl bromides bearing both electron-donating and electron-withdrawing groups have been studied, and sterically demanding aryl bromides have also been coupled in good yields.[87] For example, the reaction of 4-bromoacetophenone and 4-methylbenzeneboronic acid furnished the desired product **40** in excellent yield. MW heating for 5 min provided yields comparable to those on conventional heating for 5 h with 4-bromoacetophenone. With unactivated and deactivated aryl bromides, conventional heating was not efficient after 16 h.

The new homogeneous stable benzothiazole-based Pd(II) precatalysts **41** and **42** were efficient and highly active for the Suzuki-Miyaura and Heck-Mizoroki cross-coupling

reactions of activated aryl bromides both thermally and under MW conditions in water.[88] The immobilized catalyst **42** proved to have high longevity relative to the mobile form **41**.



41 **42**

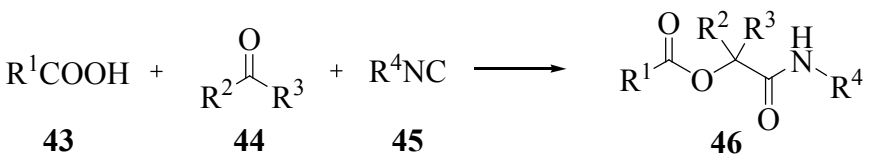
Figure 1. Precatalyst 41 and its immobilized form 42

2.3. Multicomponent reactions (MCRs) in aqueous medium

2.3.1. General aspects of MCRs

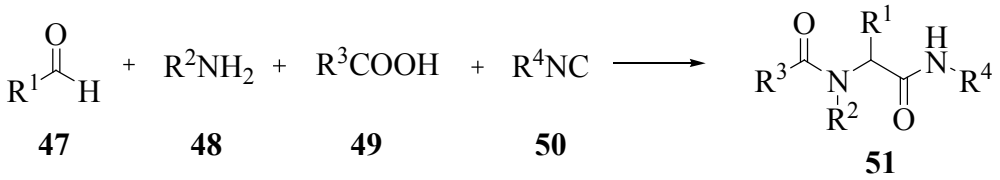
MCRs are convergent reactions in which three or more starting materials interact virtually all or most of the atoms contributing to the newly formed product. The first MCRs were accomplished by Laurent and Gerhardt in 1838, forming the benzoylazotide from bitter almond oil (a benzaldehyde source), NH_3 and HCN. The chemistry of the MCRs officially began with the Strecker synthesis, reported in 1850,[89] followed by several named MCRs, such as the Hantzsch reaction, the Mannich condensation, the Biginelli reaction and the Bucherer-Bergs reaction.[90]

Isocyanides play a dual role as they are nucleophiles and electrophiles, allowing interesting MCRs to be carried out. The first isocyanide-based MCR was discovered by Passerini in 1921.[91, 92] This three-component reaction between a carboxylic acid **43**, a carbonyl compound such as a ketone or aldehyde **44**, and an isocyanide **45** offers direct access to α-hydroxycarboxamides **46** (Scheme 14).



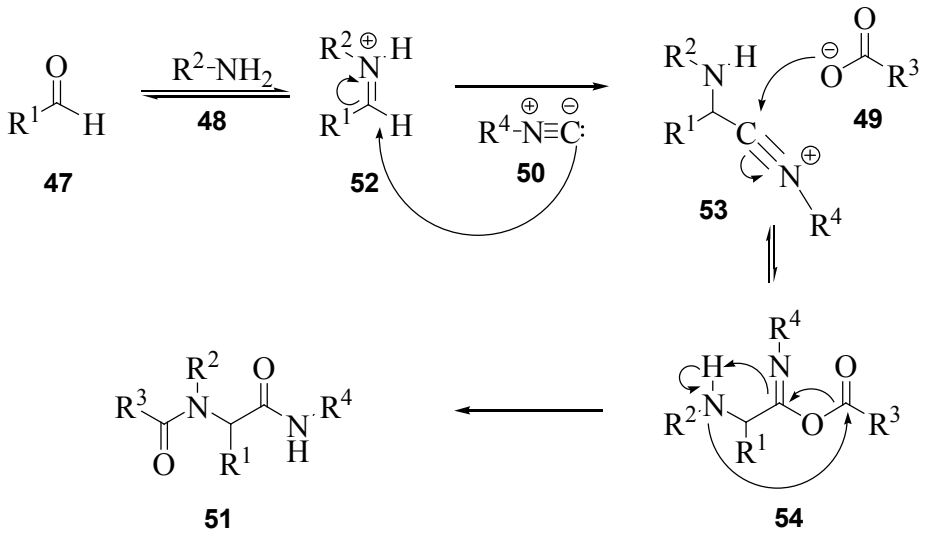
Scheme 14

In 1958, the isocyanides became generally available, and shortly afterwards Ugi introduced the four-component reaction of the isocyanides, which has been referred to as the U-4CR since 1962. Three subtypes of Ugi reaction exist: the Ugi-4-component condensation (U-4CC), the U-4C-3CR and the U-5C-4CR. The traditional U-4CC between an aldehyde **47**, an amine **48**, a carboxylic acid **49** and an isocyanide **50** allows the rapid preparation of α-aminoacyl amide **51** derivatives or various heterocycles, such as benzodiazepines, benzothiazepinones, oxazoles or isoxazoles, α-aminobutyrolactones or naturally-occurring alkaloids in high yields and high stereoselectivities (Scheme 15).[93-98]



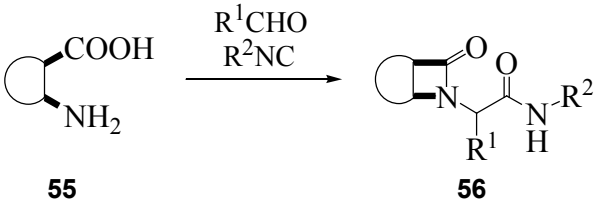
Scheme 15

The initial step in the Ugi reaction, is the formation of imine **52** from an aldehyde **47** (or ketone) and an amine **48**. Subsequent reaction of imine **52** with isocyanide **50** gives the intermediate nitrilium ion **53**, which reacts with carboxylate ion **49**. The resulting acylated isoamide **54** rearranges by acyl transfer to generate the final product **51** (Scheme 16).



Scheme 16

The intramolecularU-4C-3CR and U-5C-4CR in which the α- or β-amino acids used as starting materials contain two functional groups in the same compound, may furnish α-amino acid derivatives and β-lactams.[99-102] The most commonly used and cited reaction type is the U-4C-3CR, in which *N*-substituted β-lactams **56** are generated from *cis*-cycloalkane/enes and bicyclic *diendo*- or *diexo*-β-amino acids **55**.

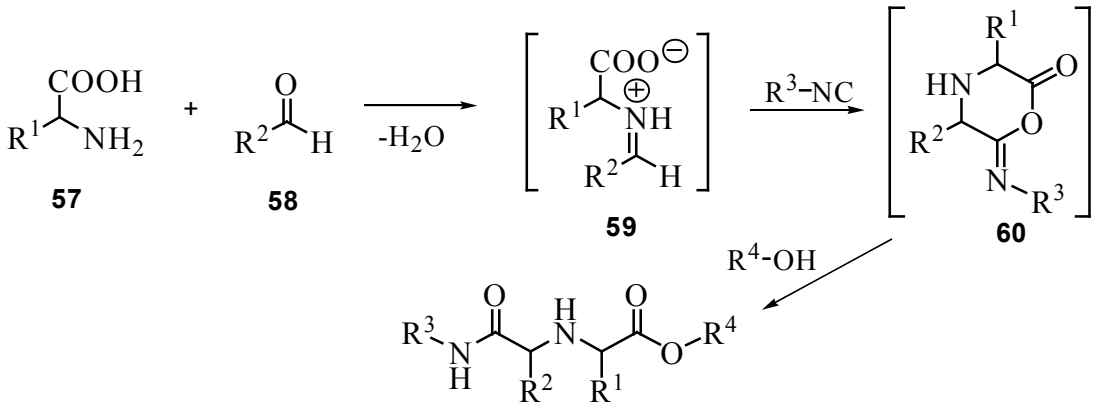


55 56

: *cis*-cyclopentane, -cyclohexane, -cyclohexene
diexo-norbornane, -norbornene
R^1 = Et, *n*Pr, Ph, *p*-OMePh
R^2 = *t*Bu, cyclohexyl, Bz

Scheme 17

Starting from *α*-amino acids, or *trans*-alicyclic or *exo-endo* bicyclic *β*-amino acids, Ugi adducts, *e.g.* *α*- and *β*-amino acid ester derivatives, can be obtained via the U-5C-4CR. Through the generation of a Schiff base **59**, an oxazinone **60** is formed which reacts with molecules of the solvent, *e.g*. MeOH in the next step. As the carboxyl and amino groups are situated relatively distant from each other, intramolecular cyclization (similarly to the U-4C-3CR) can not occur, and the reaction furnishes linear products (Scheme 18).



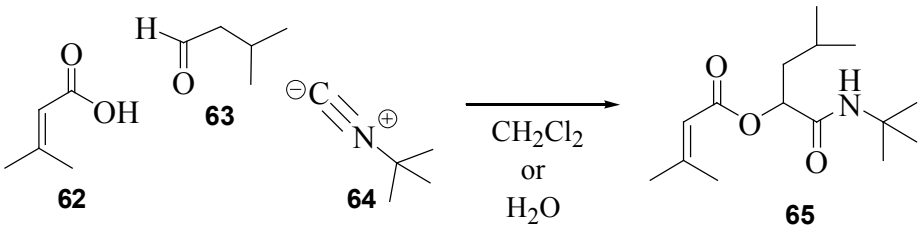
57 58 59 60 61

Scheme 18

2.3.2. Isocyanide-based MCRs in aqueous medium

While the effective formation of imines in the reactions of a wide range of aldehydes and amines in aqueous media has long been known,[103] the influence of water on the rates of MCRs such as the Passerini and Ugi reactions was examined only more recently. In 2004,

Pirrung and Das Sarma first described aqueous Ugi and Passerini reactions.[104, 105] The Passerini reaction was investigated under various conditions (Scheme 19). Although the reaction gave good results (conversion and yield) in CH_2Cl_2, the aqueous medium provided an approximately 18-fold acceleration over CH_2Cl_2. This acceleration was attributed primarily to the hydrophobic effect, enhanced hydrogen bonding in the transition state and the high cohesive energy density of water (550.2 cal mL^{-1} at 25 ºC).



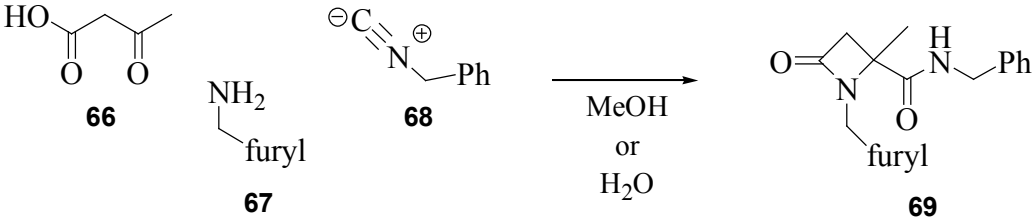
Scheme 19

Table 3. Passerini reaction (Scheme 19) under various reaction conditions

Solvent	Time (h)	Temperature (°C)	Conversion (%)	Yield (%)
CH_2Cl_2	18	25	50	45
H_2O	**3.5**	**25**	**100**	**95**
1.0 M aq. LiCl	0.8	25	100	95
0.5 M aq. glucose	2	25	100	94

Ionic and non-ionic solutes such as LiCl and glucose can increase the hydrophobic effect. In some MCRs the effects of these solutes were examined (Table 3). In the case of LiCl, the reaction displayed a 16-fold acceleration, while glucose demonstrated an additional 7-fold acceleration over pure water. Monitoring of the effects of temperature, revealed an 11% increase in the rate at 4 ºC and a 44% decrease at 50 ºC.

The widespread applicability of the accelerating effect of water was confirmed by an acceleration of ~ 50-fold for the Ugi reaction. The Ugi reaction also worked well with *β*-keto acids in aqueous medium, through the reactions were unsuccessful in different organic solvents (Scheme 20).



Scheme 20

The method for the acceleration of MCRs was used to synthetize a 32-compound Passerini product library and a 48-compound Ugi reaction library. Additionally, Pirrung and Das Sarma investigated the U-4C-3CR of aliphatic *β*-amino acids in water. The lactams were obtained in 70-99% purity and in 71-89% yields in 3 days. The synthesis of strained *β*-lactams was achieved by means of *β*-keto acids.

A 10-membered oxabicycloheptene-based *β*-lactam library was synthetized via the U-4C-3CR in water and in MeOH in order to compare the yields, diastereoselectivities and reaction conditions (Figure 2).[106] The *β*-lactams generated were obtained in 43-76% yields after 3 days in MeOH, and the diastereomeric ratio of the crude products ranging from 56:44 to 87:13. In water, the condensations were completed in 3 h to 1 day resulting in precipitated products (47-71% yields) which were isolated by simple filtration. It was observed that the concentration was a determinating factor as concerns the precipitation process.

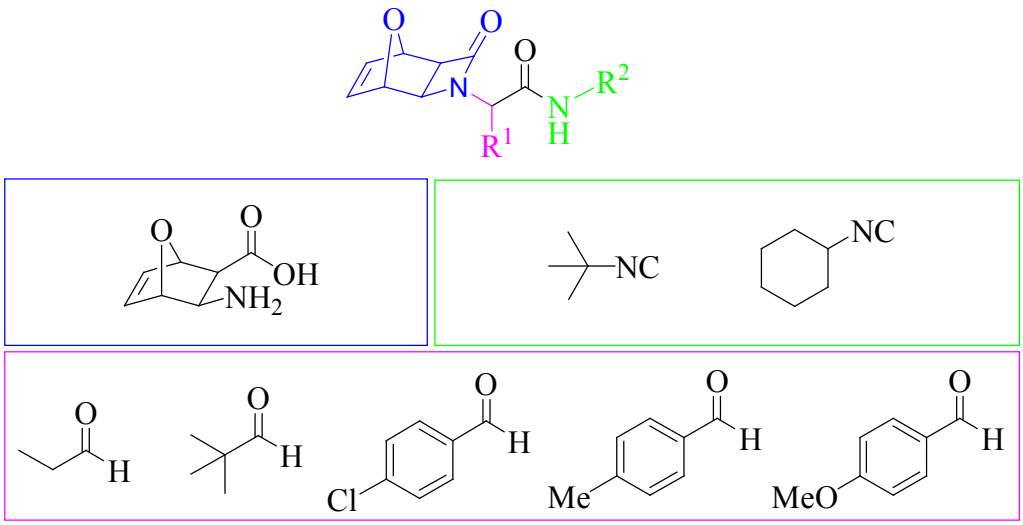
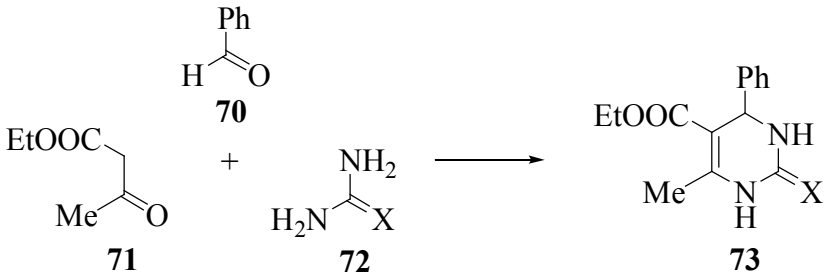


Figure 2. Building blocks of 10-membered Ugi library

2.3.3. Other MCRs in aqueous medium

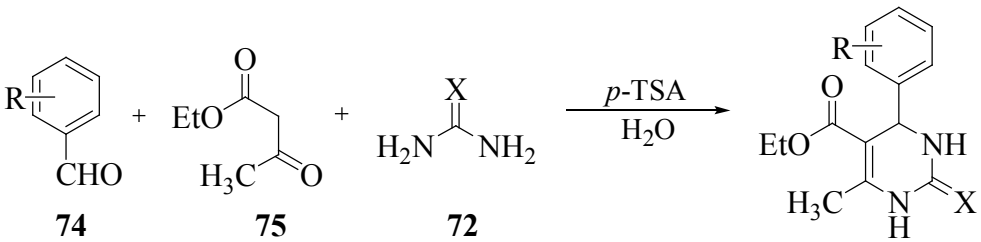
The Biginelli reaction is MCR that furnishes 3,4-dihydropyrimidin-2(1*H*)-ones **73** from an aldehyde **70**, a *β*-ketoester **71**, and a urea or thiourea **72** in the presence of a catalyst (Scheme 21). In recent years, increasing attention has been focused on the synthesis of dihydropyrimidinone derivatives because of their physiological effects.



X = O or S

Scheme 21

Bose *et al.* reported the large scale synthesis of dihydropyrimidinone derivatives **76** by using water-based biphasic reactions of immiscible organic reagents.[107] The essence of the method was the dynamic mixing of the two phases. In all cases, the corresponding *N*-heterocycles crystallized out quickly (< 30 min) from the mixture, affording an easy isolation in essentially pure form and in > 90% yield.

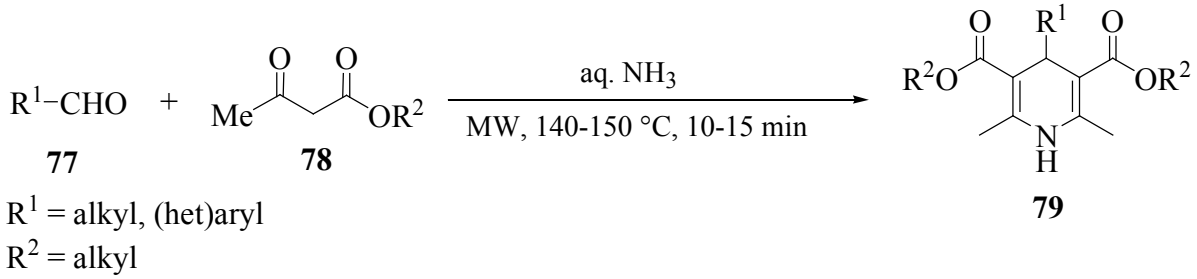


R = H, 4-OH, 4-OMe, 4-NO_2, 4-Cl
X = O or S

Scheme 22

A well-known procedure for the preparation of dihydropyridine (DHP) derivatives **79** is the one-pot condensation of an aldehyde **77** and a *β*-ketoester **78** in the presence of NH_3 in

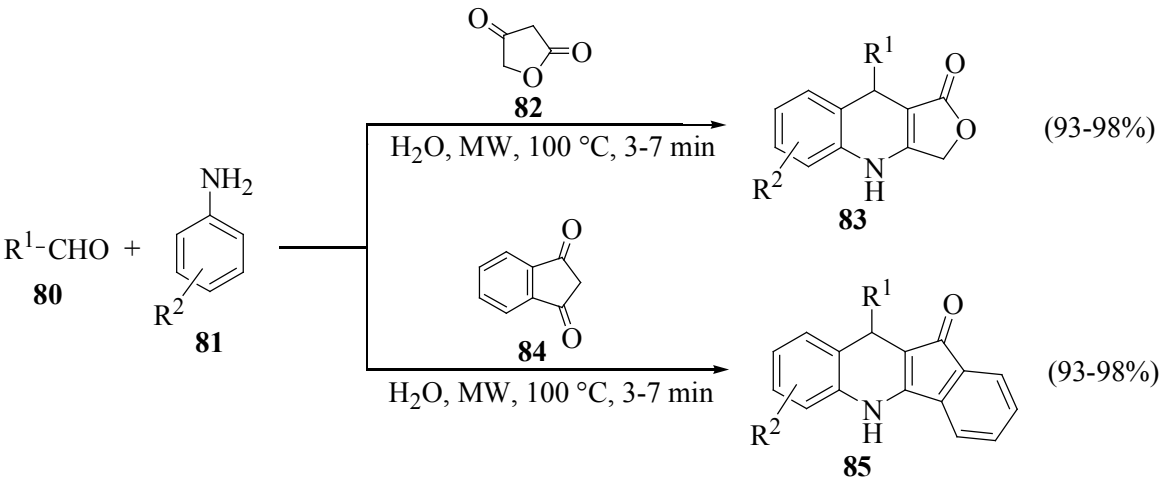
the Hantzsch reaction. Öhberg and Westman used aqueous NH_3 both as reagent and as solvent for the MW synthesis of DHP (Scheme 23).[108] A small library of 24 compounds was prepared 39-92% yields by applying an automated MW instrument in.



Scheme 23

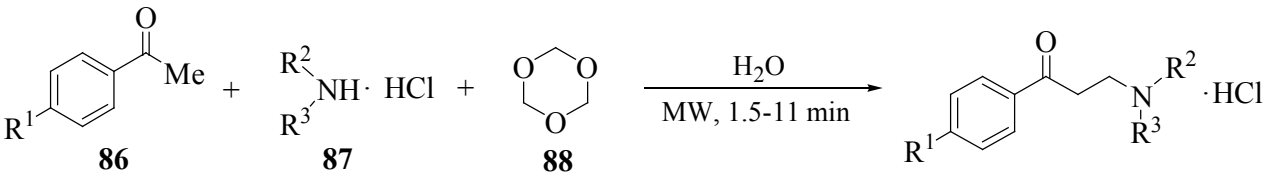
Bagley and Lubinu[109] recently reported the synthesis of DHP analogues by applying the same reaction conditions as reported by Öhberg and Westman.[108] These DHPs could be further aromatized in merely 1 min at 100 ˚C under MW irradiation to obtain the desired pyridines in excellent yields (91-100%).

Tu *et al.* have described the synthesis of 4-azapodophyllotoxin derivatives **83** and **85** via the one-pot condensation of an aldehyde **80**, an aromatic amine **81** and tetronic acid **82** or 1,3-indanedione **84** (Scheme 24).[110] When the reaction conditions were optimized, the volume of water applied as solvent proved crucial for the outcome of the reaction. Through use of this method, a set of 4-azapodophyllotoxin derivatives **83** and **85** could be generated in a very short reaction time in high yields.



Scheme 24

The Mannich reaction is one of the most important transformations leading to *β*-amino ketones. This MCR suffers from some disadvantages, such as the need for forcing conditions, long reaction times and sometimes low yields of the products. Peng *et al.* reported on the Mannich reaction of acetophenones **86**, secondary amines **87** as hydrochloride salts, and 1,3,5-trioxane **88** as formaldehyde source (Scheme 25).[111] *β*-Amino ketones **89** were generated in 50-80% yields in 1.5-11 min under MW irradiation. A combination of MW conditions and ultrasound resulted in shorter reaction times (20-50 s) and higher yields.[112]



86 **87** **88** **89**

R^1 = H, NO_2

R^2 = R^3 = Me, Et

piperidine, morpholine, pyrrolidine

Scheme 25

3. RESULTS AND DISCUSSION

3.1. Syntheses and transformations of novel *β*-amino acid derivatives of enantiomeric monoterpenes

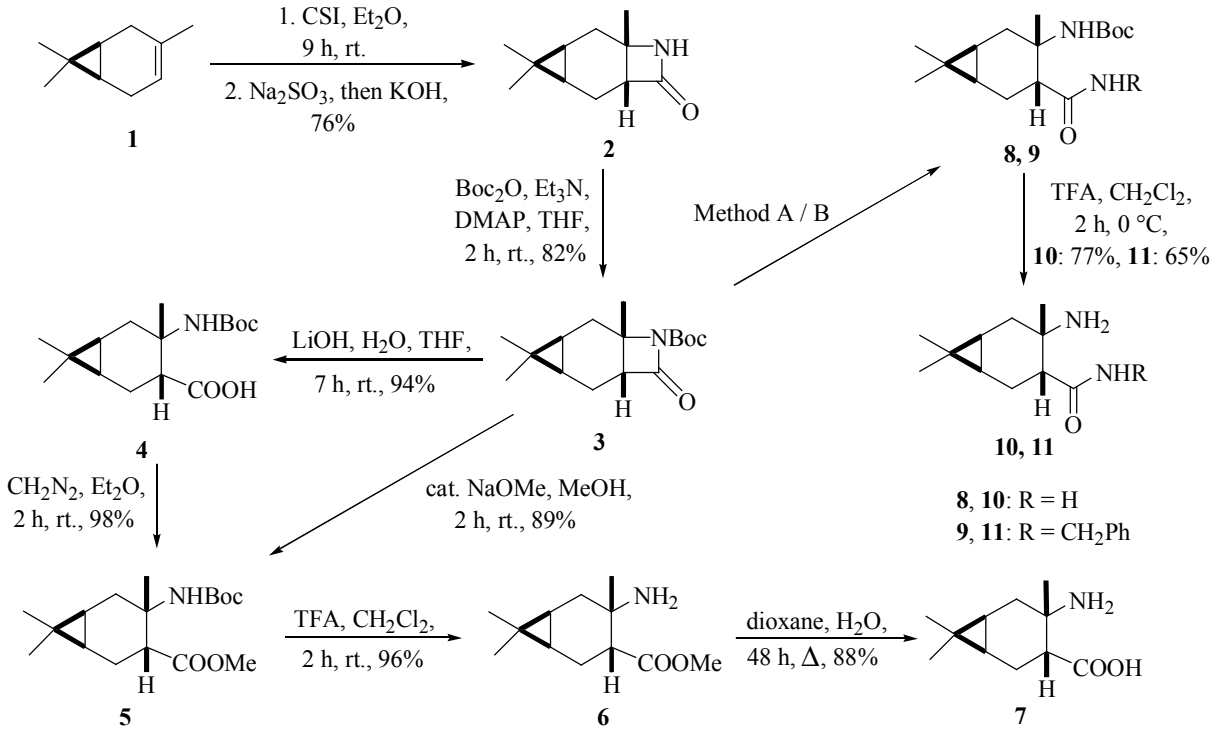
The readily available terpene enantiomers and their derivatives are widely used as chiral auxiliaries in enantioselective transformations.[113] Various powerful catalysts derived from monoterpenes, such as (+)-pulegone,[114] *β*-pinene,[115] nopinone,[116] fenchone-camphor,[117] limonene[118] and recently (+)-3-carene,[119] have been reported to have been successfully used as chiral ligands in enantioselective syntheses.[120] An earlier publication describes the transformations of enantiomerically pure *α*-pinene to *β*-amino acid derivatives such as amino esters and amino alcohols.[121] The synthesis and transformations of a new family of monoterpene-based chiral *β*-lactams and *β*-amino acid derivatives were investigated by using (+)- and (–)-*δ*-pinene.[122] Amino alcohols derived from *β*-amino acids proved to be excellent building blocks for the synthesis of monoterpene-fused saturated 1,3-heterocycles and were also applied as chiral auxiliaries in the enantioselective reactions of Et_2Zn with aromatic aldehydes.[123, 124]

The aim was to synthetize novel chiral *β*-amino acid derivatives starting from the commercially available monoterpene (+)-3-carene **1**. We focused on different ring-opening reactions of the corresponding *β*-lactam **2** and some cyclization reactions to create new monoterpene-fused saturated 1,3-heterocycles.

The well-known chlorosulfonyl isocyanate (CSI) reaction was applied to prepare the desired cycloalkene-fused *β*-lactam **2**. There are numerous publications regarding the regio- and stereoselectivity of the cycloaddition, which proceeds in accordance with the Markovnikov orientation of the CSI addition.[125] The *exo* stereoselectivity of the CSI addition was proved earlier in the publication of Sasaki *et al.*[126] Due to the *ab initio* theoretical results of Cossio *et al.*,[127] the [2+2] cycloaddition proceeds via an asynchronous transition state where the partial positive charge attacked by the N atom is significantly stabilized by any electron-donating substituent.[128] For 3-carene **1,** the attached Me substituent can exert a stabilization effect, which rationalizes both the faster reaction towards *β*-lactam **2** and the regiospecifity of the reaction.

Several procedures are to be found in the literature concerning the different ring-opening reactions of azetidinones.[22, 129, 130] First, acidic hydrolysis of azetidinone **2** was attempted by using aqueous HCl to prepare the amino acid; next, **2** was refluxed with EtOH containing HCl to obtain the corresponding amino ester. None of the applied methods resulted in the expected compounds: only a mixture of several decomposed products was obtained. These experiments suggested that the strongly constrained carene ring system breaks down under highly acidic conditions, similarly to α-pinene derivatives.[131] Nevertheless, the successful acidic ring-opening reaction of the β-lactam derived from δ-pinene proved the significance of the position of the electron-donating Me group relative to the double bond.[122] This points to the fact that the opening of the β-lactam ring could be achieved only through nucleophilic attack in an alkaline environment. Therefore, it was necessary to activate the carboxamide bond of the β-lactam **2** with a *tert*-butyloxycarbonyl (Boc) protecting group, resulting in *N*-Boc-β-lactam **3**, which could be opened under mild conditions to give the corresponding amino ester or other Boc-protected amino acid derivatives. The synthesis of *N*-Boc-amino ester **5** was carried out in two different ways. *N*-Boc-lactam **3** was the key intermediate. First, *N*-Boc-amino acid **4** was prepared from *N*-Boc-β-lactam **3** in excellent yield with aqueous LiOH in tetrahydrofuran (THF), followed by esterification to *N*-Boc-amino ester **5**. In the second pathway, the base-catalysed ring opening of lactam **3** afforded **5** in one step. After elimination of the Boc protecting group, the resulting β-amino ester **6** was transformed to β-amino acid **7** in good yield by refluxing in a dioxane:water = 1:1 mixture for 2 days.

The nucleophilic ring opening of *N*-Boc-β-lactam **3** was also performed with different amines, such as NH_3 and $PhCH_2NH_2$, deprotection of the intermediate *N*-Boc-amides **8** and **9** resulting in amides **10** and **11** (Scheme 1).



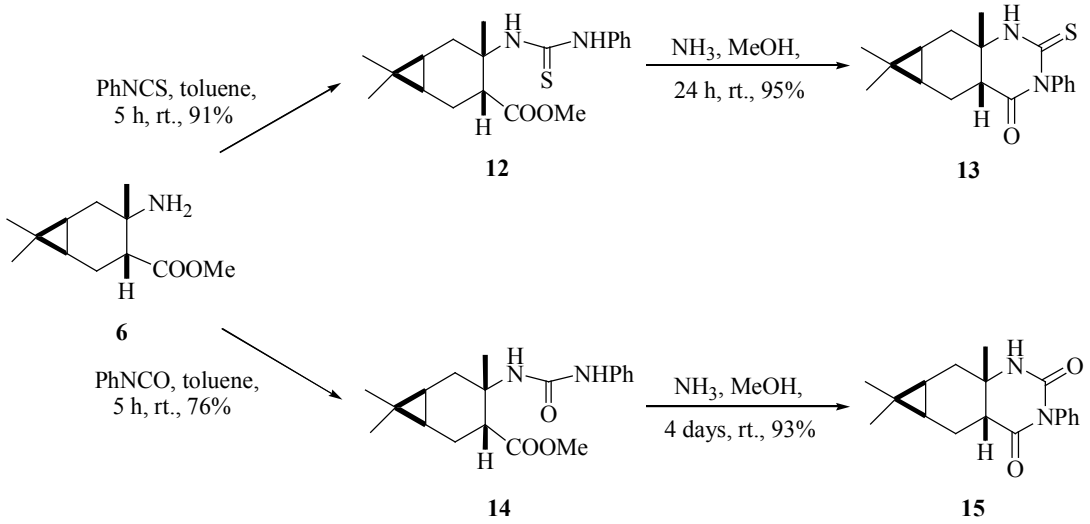
Method A: NH_3, MeOH, 12 h; 4 °C; 60%; Method B: $PhCH_2NH_2$, KCN, DMF, 24 h; 40 °C; 78%.

Scheme 1. Synthetic route to novel *β*-amino acid derivatives 4-11

The further transformations of *β*-amino ester **6** with phenyl isocyanate or phenyl isothiocyanate led to thiourea **12** and urea **14**, which were easily cyclized in the presence of a catalytic amount of NH_3[121] to 2-thioxo-4-pyrimidinone **13** and 2,4-pyrimidinedione **15** (Scheme 2). A series of pyrimidinone compounds were examined and proved to inhibit HIV integrase and thereby prevent viral integration into human DNA. This action makes the compounds useful for the treatment of HIV infection and AIDS.

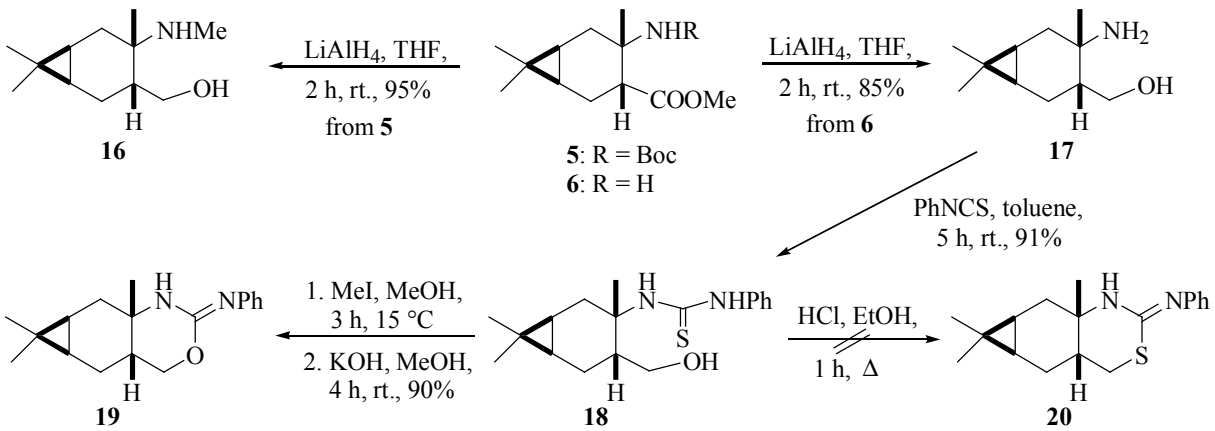
The *β*-amino acid derivatives prepared are potentially valuable building blocks for the asymmetric synthesis of potential pharmacons, *β*-amino acid oligomers and modified analogues of natural peptides. They may also serve as chiral auxiliaries and catalysts in enantioselective syntheses.

Amino ester **6** was converted to amino alcohol **17** by $LiAlH_4$ reduction. The *N*-Me analogue of amino alcohol **17** was also prepared by $LiAlH_4$ reduction from *N*-Boc-amino ester **5**. Enantiomeric *β*-amino acid derivatives such as 1,3-amino alcohols are well-known starting materials for the synthesis of efficient ligands[132] in a wide range of enantioselective syntheses.[133, 134]



Scheme 2. Conversion of *β*-amino ester 6 to pyrimidinone 13 and pyrimidinedione 15

We have also used phenyl isothiocyanate to produce thiourea adduct **18** from amino alcohol **17**. The ring closure of **18** with MeI resulted in 2-phenylimino-1,3-oxazine **19**, following alkaline MeSH elimination. The acid-catalysed ring closure of thiocarbamide adducts of 1,3-amino alcohols is a well-known procedure for the preparation of 2-imino-substituted 1,3-thiazines.[135] Accordingly, the transformation of thiocarbamide **18** to thiazine **20** was also attempted, but, probably because of the acidic conditions, the reaction failed (Scheme 3).



Scheme 3. Synthesis and transformation of amino alcohols 16 and 17

Although (+)-3-carene proved to be a valuable starting material for the synthesis of different 1,3-bifunctional, 1,3-disubstituted chiral building blocks in high enantiomeric purity,

its disadvantage is that only one enantiomer is available. Since the original asymmetry centres of 3-carene were not affected by the transformations applied and there was no sign of the presence of any other diastereomer in the NMR spectra of the crude products, the high enantiomeric purity of the compounds prepared can be regarded as certain.

3.2. Synthesis of 3- and 4-hydroxy-substituted amino acids

Although alicyclic saturated amino acids have proved to be of great importance, their partially saturated analogues give scope for further functionalization of the alicyclic ring, *e.g.* one or two hydroxy groups have been incorporated. Formation of the helical structure of *β*-peptides is strongly influenced by the nature and stereochemistry of the amino acid side-chain at both the *α* and *β* positions. In 2001, Tromp *et al.* reported on the synthesis of *α*-hydroxylated *β*-oligopeptides, the NMR studies strongly indicating that no helical structure is formed in pyridine.[136] In contrast, Gellman *et al.* observed that oligomers composed of 3-methoxy- or 3-phenoxy-substituted *trans*-ACPC residues maintain the 12-helical conformation displayed by the nonsubstituted analogues.[137] Thus, the presence of unprotected *α*-hydroxy groups exerts a great influence on the formation of the secondary structure. Hydroxyamino compounds may also serve as building blocks in the synthesis of peptides, peptidomimetics and various heterocycles; they can take part in enzymatic transformations and provide scaffolds for combinatorial chemistry.[138]

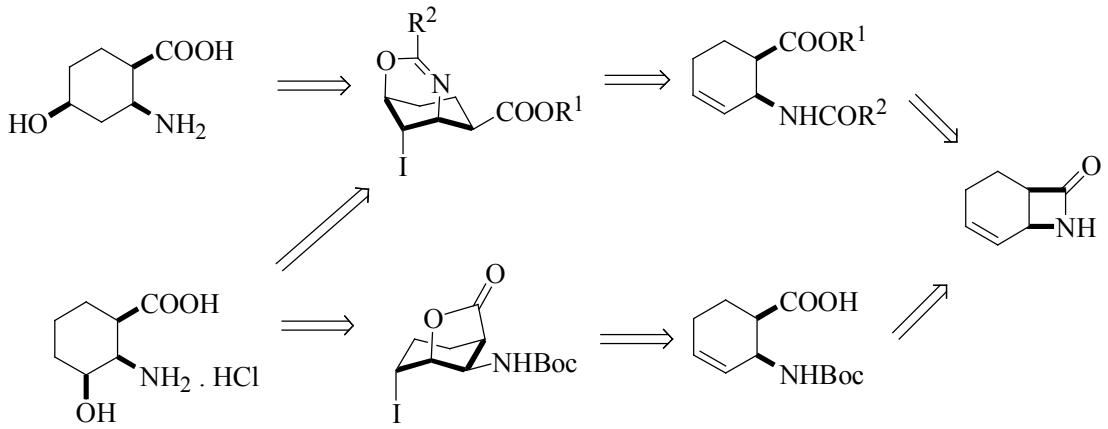
The hydroxy-*β*-amino acid unit is the essential moiety of several familiar, naturally-occurring products that possess powerful biological activity. For example, Taxol derivatives,[139] the immunological response modifier dipeptide bestatin,[140] amastatin[141] and the highly potent HIV-1 protease inhibitor kynostatins[142, 143] contain an *α*-hydroxy-*β*-amino acid unit.

In recent years, the regio- and diastereoselective functionalization of *cis*- and *trans*-2-amino-4-cyclohexenecarboxylic acids has been reported, resulting in the synthesis of 2-amino-4-hydroxycyclohexanecarboxylic acid and its 5-hydroxy-substituted analogue via 1,3-oxazine and γ-lactone intermediates.[144]

The first isolated alicyclic hydroxy-*β*-amino acid oryzoxymycin was extracted from a *Streptomyces* species by Hashimoto *et al.*.[145, 146] In 2003, Bunnage *et al*. reported the asymmetric synthesis of (-)-oryzoxymycin.[147] In work relating to this thesis, one of my main projects was the synthesis of saturated analogues of oryzoxymycin via iodooxazine or iodolactone intermediates.

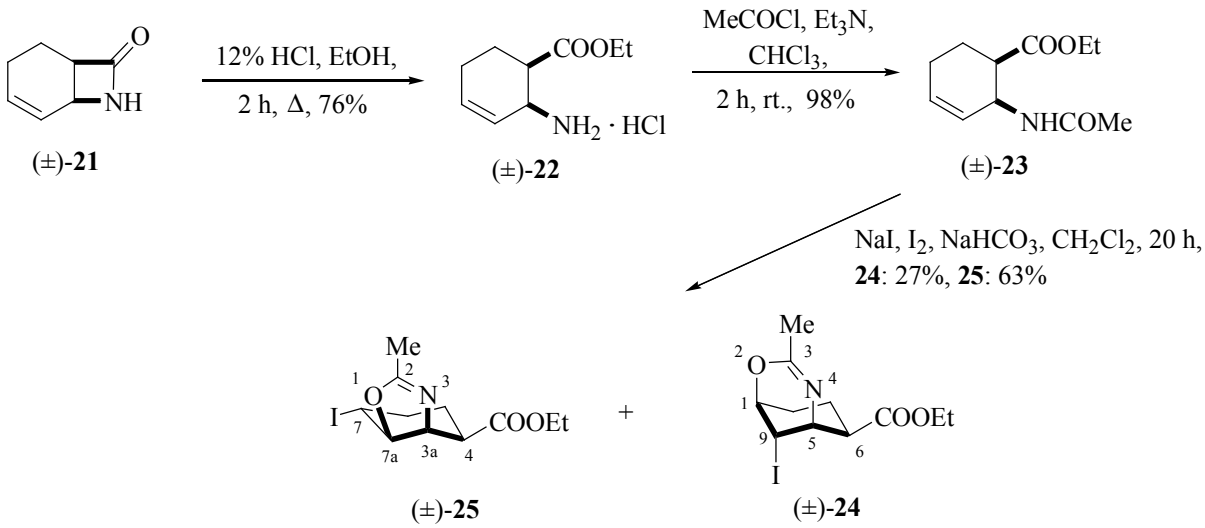
If the desired iodocyclization methods are applied to *cis*-2-amino-3-cyclohexenecarboxylic acid derivatives, two synthetic pathways are available to obtain 3- and

4-hydroxyamino acids.[148] The cyclization can be accomplished by attack on the activated double bond by the amide carbonyl, resulting in *O,N* heterocycles. Similarly, a five- or six-membered lactone ring can be achieved by starting from the *N*-Boc-protected amino acid (Scheme 4).



Scheme 4. Retrosynthetic pathway of the synthesis of hydroxy-substituted amino acids

β-Lactam **21** was synthetized from 1,3-cyclohexadiene in acceptable yield (60%) by a literature method.[149] Then transformed to the corresponding amino ester hydrochloride salt **22** with EtOH containing dry HCl. After acylation of amino ester **22**, the *N*-acylamino ester **23** obtained was cyclized with I_2 and NaI in a two-phase solvent system, resulting in *O,N* heterocycles **24** and **25**. The regioselectivity of the iodocyclization reaction was moderate: the ratio of iodooxazine **24** and iodooxazoline **25** isomers was 30:70 (Scheme 5).



Scheme 5. Iodocyclization reaction resulting in *O,N* heterocycles (±)-24 and (±)-25

The structural isomers were succesfully separated and fully characterized by NMR measurements. The relative positions of the iodine atoms were deduced from the *J* couplings and NOESY spectra. The structures were confirmed by molecular modelling. The conformational protocol comprised a stochastic search using the Merck molecular force field (MMFF94).

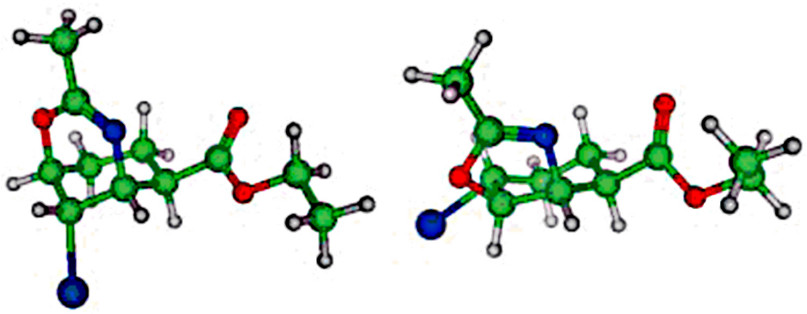
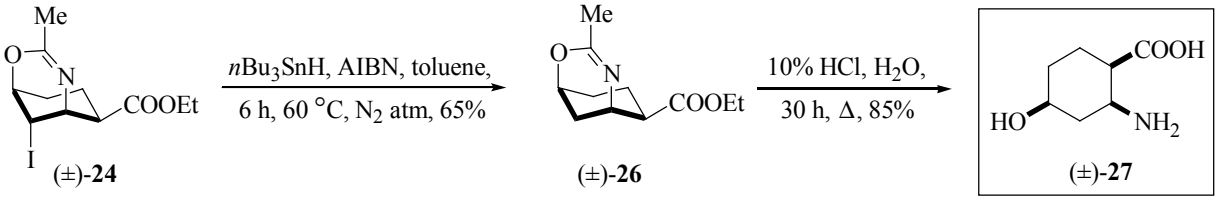


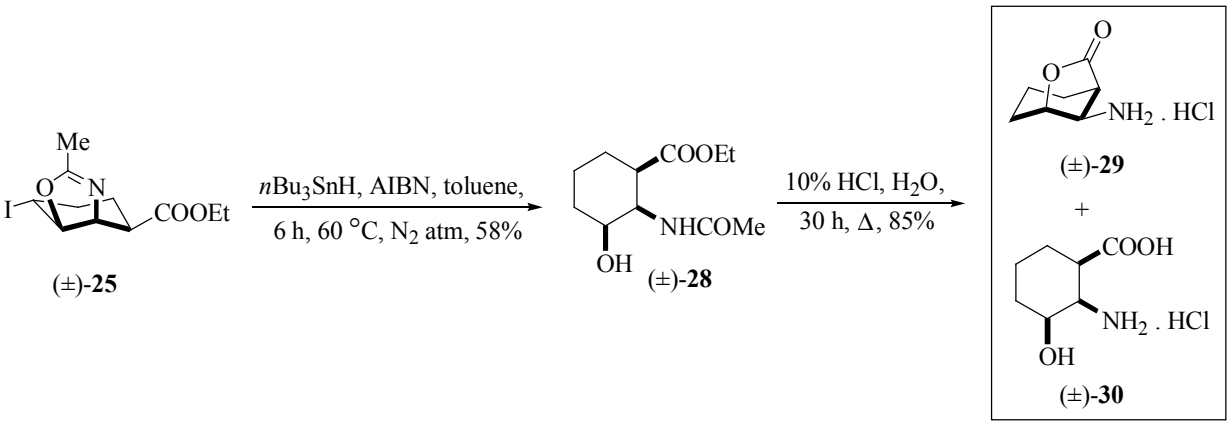
Figure 1. Stereoview of typical minimum-energy molecular structures of 24 and 25

Both of the iodo-substituted compounds **24** and **25** were dehalogenated with nBu$_3$SnH in the presence of a catalytic amount of azobis(isobutyronitrile) (AIBN) under a N_2 atmosphere. After deiodination of oxazine **24**, **26** was hydrolysed to the desired 4-hydroxyamino acid **27** by refluxing with aqueous HCl (Scheme 6).



Scheme 6. Synthesis of 4-hydroxy-substituted amino acid 27

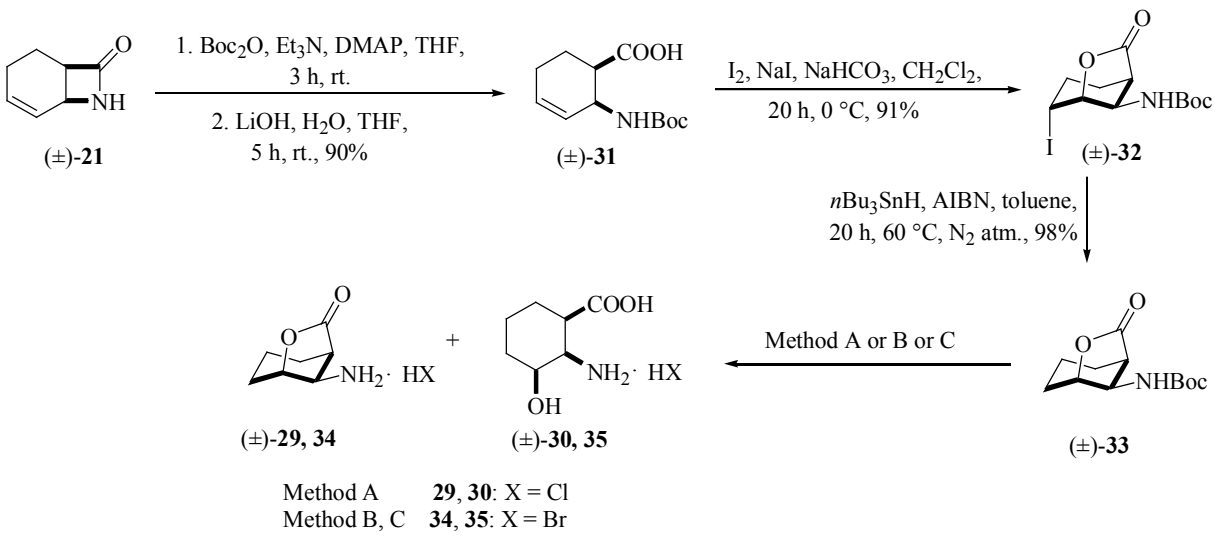
When the dehalogenation of oxazoline **25** was attempted, under the conditions applied only the ring-opened *N*-acetylamino ester **28** could be isolated. Hydrolysis of **28** with aqueous HCl resulted in a mixture of amino lactone **29** and 3-hydroxy-substituted *β*-amino acid **30** (Scheme 7).



Scheme 7. Synthesis of 3-hydroxy-substituted amino acid 30

Since the procedure described above was not so effective as we had expected (*e.g.* inappropriate selectivity, more reaction steps, and low overall yield) and furnished only the 4-hydroxy derivative **27**, our attention turned to the iodolactonization protocol.

The alternative synthetic route also started from *β*-lactam **21.** After Boc protection of *β*-lactam **21**, the *N*-Boc compound obtained was hydrolysed with aqueous LiOH in THF to give the unsaturated *N*-Boc-*β*-amino acid **31**. The iodolactonization of **31** furnished the five-membered lactone ring-containing **32** in a stereo- and regioselective cyclization, in excellent yield (91%). Deiodination of **32** gave *N*-Boc lactone **33** nearly quantitatively after 20 h at 60 ˚C (Scheme 8).



Method A: HCl, H_2O, 12 h, rt.; Method B: HBr, H_2O, 12 h, rt.; Method C: Me_3SiBr, PhOH, CH_2Cl_2, 2 h, rt., Ar atm, 65%.

Scheme 8. Synthesis of 3-hydroxyamino acids (±)-30 and (±)-35 and amino lactones (±)-29 and (±)-34 via iodolactone 32

During the hydrolysis of *N*-Boc-lactone **33** with different acidic reagents, a varied mixture of hydroxyamino acid **30** or **35** and deprotected stable amino lactone **29** or **34** was obtained. The use of Me_3SiBr and PhOH for the deprotection of amino lactone **33** led to the formation of only the amino lactone **34** (Table 1).

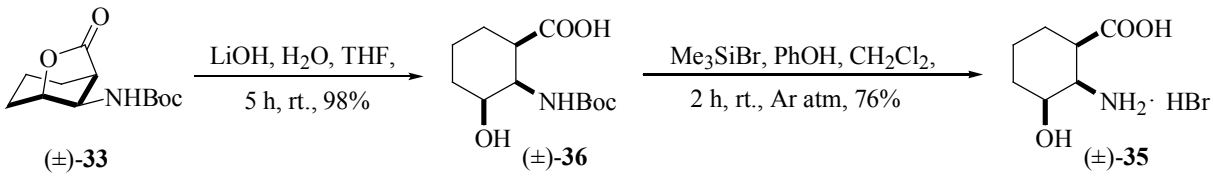
Table 1. Product ratio after the deprotection and hydrolysis of *N*-Boc-amino lactone (±)-33

Method[a]	Ratio of amino lactone and hydroxyamino acid
Method A	**(±)-29:(±)-30** = 23:77
Method B	**(±)-34:(±)-35** = 15:85
Method C	**(±)-34:(±)-35** =100:0

a: See Scheme 8.

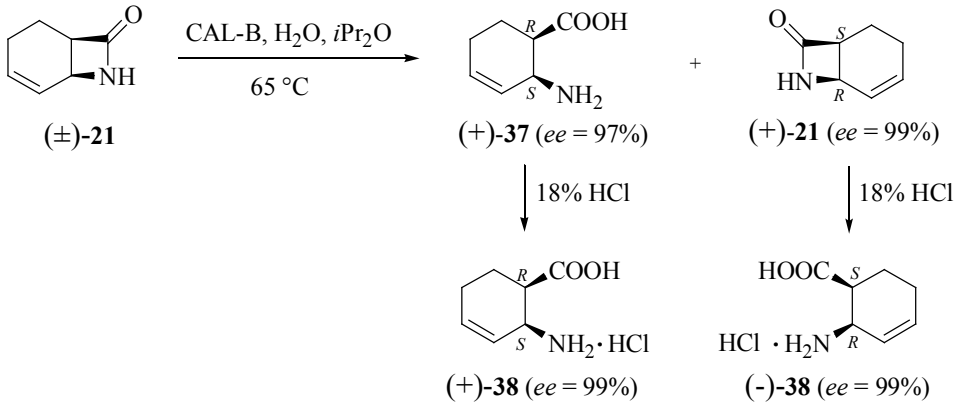
When the hydrolysis of *N*-Boc-amino lactone **33** was attempted with aqueous LiOH in THF, the expected *N*-Boc-hydroxyamino acid **36** was obtained in excellent yield (98%). Removal of the Boc protecting group was achieved similarly as in the deprotection protocol

of amino lactone **33,** the 3-hydroxy-substituted *β*-amino acid being produced as the hydrobromide **35** (Scheme 9).[150] It should be mentioned that the sequence of the reaction steps could not be changed: hydrolysis of amino lactone **33** was carried out first, followed by removal of the protecting group.On deprotection of amino lactone **33,** a stable molecule resulted, which was resistant to the applied opening protocols.



Scheme 9. Synthesis of 3-hydroxyamino acid (±)-35 from *N*-Boc-amino lactone (±)-33

In order to synthetize the enantiopure form of hydroxyamino acids **(+)-35** and **(-)-35**, the highly enantioselective *Candida antarctica* lipase B (CAL-B)-catalysed ring pening of *β*-lactam **21** was performed (E > 200) following the literature procedure (Scheme 10).[151] The enantiomers **(+)-21** and **(+)-37** were hydrolysed to the expected enantiopure cyclohexene-fused *β*-amino acid **(+)-38** and **(-)-38** as hydrochlorides. The *ee* values were determined by gas chromatography on a Chrompack Chirasil-Dex CB column. After Boc protection, the hydroxyamino acid enantiomers **(+)-35** and **(-)-35** were obtained following a procedure similar to that used for the synthesis of racemic **35** from racemic *N*-Boc-amino acid **31**.



Scheme 10. CAL-B-catalysed ring opening of *β*-lactam (±)-21 to produce enantiopure hydroxyamino acids (+)-38 and (-)-38

In conclusion, iodocyclization has proved to be a very efficient method for the synthesis of either racemic or enantiomeric 2-amino-3-hydroxycyclohexane-carboxylic acid **35**.

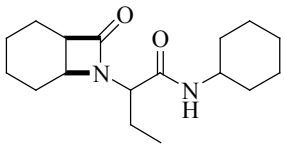
3.3. Application of the aqueous U-4C-3CR to synthetize *β*-lactams

3.3.1. Preliminary experiments

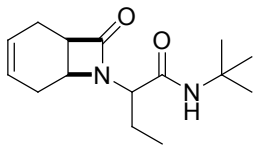
The synthesis of an Ugi library generated from bifunctional *β*-amino acids, various aldehydes and isocyanide building blocks in MeOH was recently reported.[101] The conversion was completed in 3 days at room temperature, resulting in a *β*-lactam library with high diversity.

The aim was to compare the efficiency of an aqueous medium with that of MeOH as solvent during the preparation of the analogue library. A cyclohexane-structured *β*-amino acid **II** and its unsaturated analogue **III** were first reacted with propionaldehyde **A** and two different isocyanides (*t*BuNC **a** and cyclohexyl isocyanide **b**) in water in the same procedure as used in MeOH. The results are presented in Table 2.

Table 2. Comparison of results in MeOH and aqueous medium



IIAa



IIIAb

Compound	Solvent	Time (day)	Yield (%)	Diastereomeric ratio[a]
IIAa	MeOH	3	42	3:1
	H_2O	**1**	**49**	**3:1**
IIIAb	MeOH	3	45	2:1
	H_2O	**1**	**63**	**2:1**

a: The diastereomeric ratio was determined from the NMR spectra.

As better results were obtained in aqueous medium than in MeOH, we applied eight alicyclic *β*-amino acids, four aldehydes and two isocyanides to create a novel Ugi library in water (Figure 2).

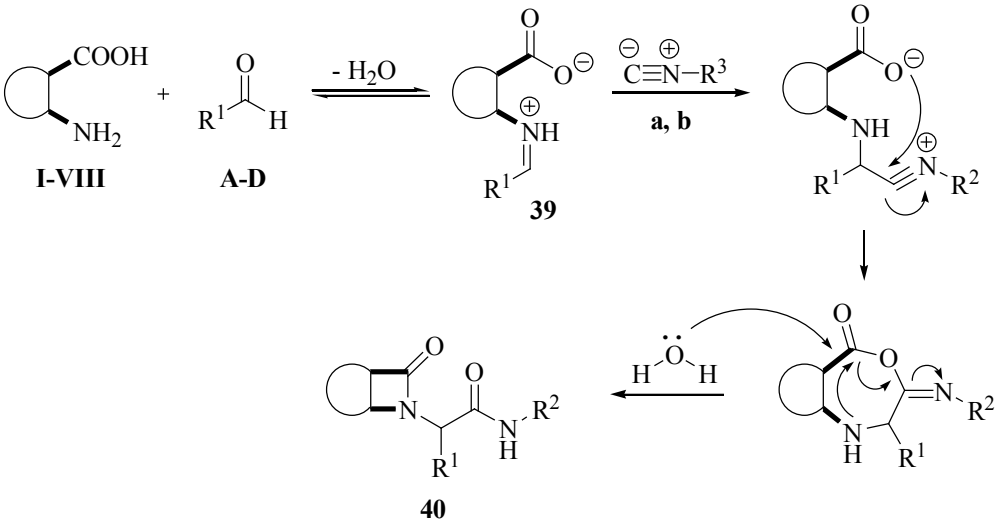
3.3.2. Synthesis of starting alicyclic *β*-amino acids (I-VIII)

The *β*-amino acids used to produce the Ugi library were synthetized by well-known literature methods. *cis*-ACPC **I** was prepared by the addition of CSI to cyclopentene, resulting in 2-chlorosulfonyl-2-azabicyclo[3.2.0]heptan-3-one, which was transformed to the azetidinone derivative with $Na_2S_2O_4$. The treatment of azetidinone with concentrated aqueous HCl, followed by ion-exchange chromatography purification, resulted in the free amino acid.[152] In the presence of aqueous NH_3, cyclohexane-*cis*-1,2-dicarboxylic anhydride was transformed to *cis*-2-carbamoylcyclohexanecarboxylic acid; subsequent Hofmann degradation with NaOBr resulted in *cis*-2-aminocyclohexanecarboxylic acid **II.**[153] For the unsaturated *cis*-6-aminocyclohex-3-enecarboxylic acid **III**, a modified Hofmann degradation with NaOCl was applied.[154] *cis*-2-Aminocyclohex-3-enecarboxylic acid **IV** was synthetized in two steps. The CSI reaction of 1,3-cyclohexadiene yielded the corresponding azetidinone, which was refluxed with 18% HCl.[149] The syntheses of *diendo*-3-aminobicyclo[2.2.1]heptane-2-carboxylic acid **V** and *diendo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid **VII** were achieved by Hofmann degradation from the corresponding anhydride. The analogous *diexo*-3-aminobicyclo[2.2.1]heptane-2-carboxylic acid **VI** and *diexo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid **VIII** were prepared by Hofmann degradation.

3.3.3. Synthesis of alicyclic *β*-lactams via the U-4C-3CR in aqueous medium

In this work, a modified U-4C-3CR was applied, which combines a bifunctional *β*-amino acid (carbonyl and amine functional groups are present simultaneously), an aldehyde and an isocyanide in a one-pot condensation. Variations in the starting compounds may lead to totally new scaffolds, including *β*-lactams, benzodiazepines, piperazines, morpholines and other derivatives.[155-160]

The mechanism is believed to involve the initial formation of an imine **39** by condensation of the amine function of *β*-amino acids **I-VIII** with the aldehyde **A-D**, followed by addition of the carboxylic acid oxygen and the imino carbon across the isocyanide carbon; intramolecular cyclization and rearrangement then afford the final azetidinone **40** (Scheme 11).



Scheme 11. Construction of azetidinones 40 from bifunctional *β*-amino acids (I-VIII) via Schiff's bases 39

A *β*-lactam library was created in aqueous medium and the reaction conditions were investigated relative to those for the reactions in organic solvent. An additional goal was to find the optimum reaction conditions for a precipitation process, facilitating the isolation of the final products.

Figure 2 shows the compounds selected to create the desired *β*-lactam library: 4 aliphatic and aromatic aldehydes (**A-D**), 8 cyclic *β*-amino acids (*cis*-2-ACPC (**I**), *cis*-2-aminocyclohexane- (**II**), 6-aminocyclohex-3-ene- (**III**), 2-aminocyclohex-3-ene- (**IV**), *diendo*-3-aminobicyclo[2.2.1]heptane-2- (**V**), *diexo*-3-aminobicyclo[2.2.1]heptane-2- (**VI**), *diendo*-3-aminobicyclo[2.2.1]hept-5-ene-2- (**VII**), *diexo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**VIII**)) and cyclohexyl isocyanide (**a**) and *t*BuNC (**b**). Because of the high number of possible combinations, only representative members of the library were prepared.

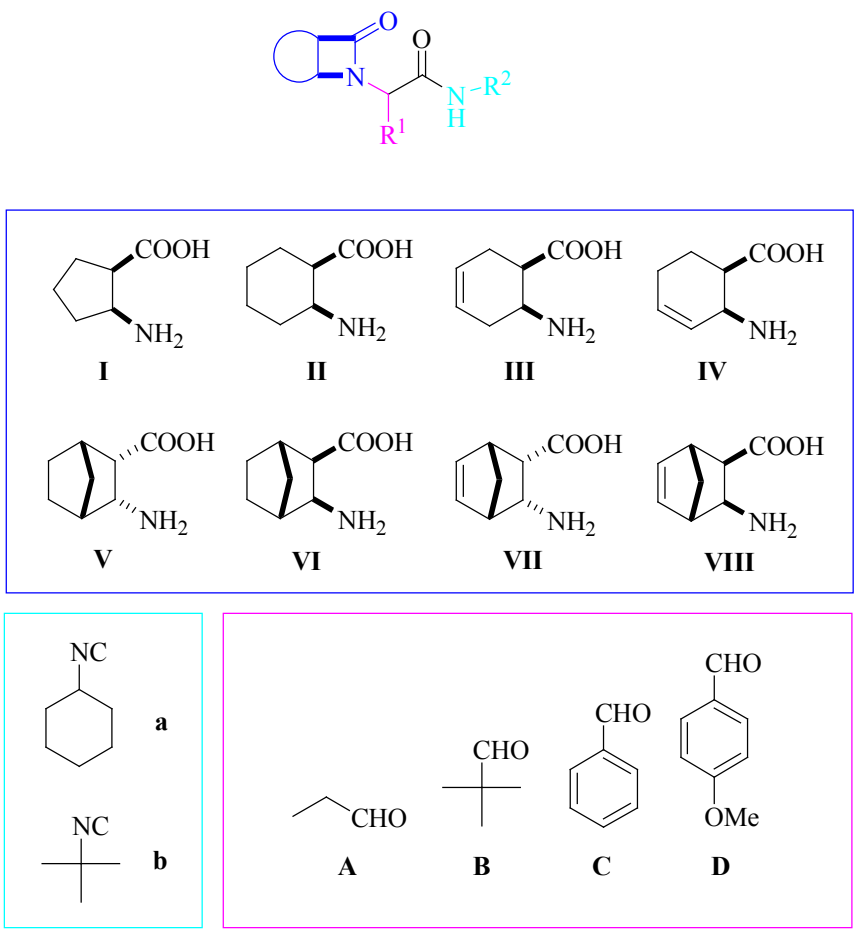


Figure 2. Building blocks of bi- and tricyclic *β*-lactam library

The general reaction mechanism is represented in Scheme 11. In the course of the experimental work, racemic *β*-amino acid **I-VIII** (10% excess) was reacted with an equimolar amount of the corresponding aldehyde (**A-D**) in a few drops of water, followed by the addition of isocyanide to the generated Schiff base. After stirring for 1 day, the precipitated product was filtered off. As indicated in Figure 3, precipitation mainly occurred for the norbornane- and norbornene-structured *β*-amino acids (**V-VIII**), aromatic aldehydes (**C, D**) and *t*BuNC (**b**).

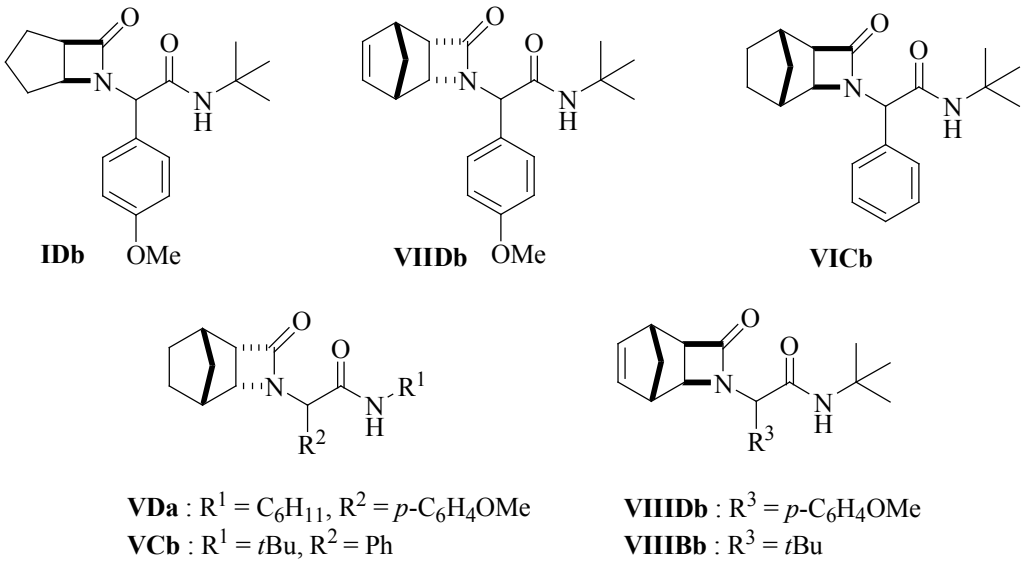


Figure 3. Products precipitated as crystals in the synthesis of the Ugi library in water

Table 3. Yield and diastereomeric ratio of crystallized product

Compound	Yield (%)	Diastereomeric ratio
IDb	38	3:1
VIIDb	48	100:0
VICb	35	92:8
VDa	47	100:0
VCb	45	100:0
VIIIDb	48	83:17
VIIIBb	51	100:0

The diversity of the final *β*-lactam library was increased thanks to the aldehyde constituent, since aldehydes are available commercially in great structural variety. However, the poorer solubility of the different aldehydes in aqueous medium reduced their applicability, *e.g. p*-nitrobenzaldehyde was unusable for the Ugi reaction in aqueous medium because of its insolubility, in contrast with its applicability in organic solvent.[101] It should be mentioned that with of anisaldehyde **D** the final products were isolated in only moderate yields, and column chromatography was necessary to remove the remaining unreacted aldehyde. With aliphatic aldehydes such as propion- and pivalaldehyde, good yields were obtained.

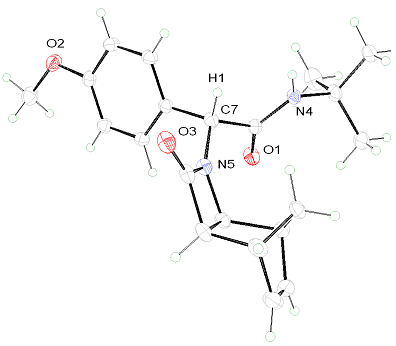
During these experiments, the concentration was the determinating factor whether the precipitation process occurred. With an appropriate amount of water, condensation was completed in 1 day at room temperature instead of 3 days in MeOH. In most cases, the crude lactams were sufficiently pure to allow analytical identification measurements and further purification was not required (except anisaldehyde **D**). The yields in aqueous medium were hardly better than those in MeOH, and the diastereomeric ratios did not differ notably in the two solvents.[101]

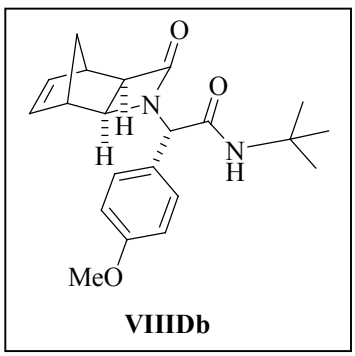
We found that the U-4C-3CR is an efficient method for the construction of a *β*-lactam library in water because of the beneficial effects on both the rate and the diastereoselectivity and the shorter reaction time. Additionally, work-up procedures may be facilitated since the final compounds could be isolated by simple filtration.

3.3.4. Diastereoselectivity of the Ugi products

In all cases, the one-pot reaction of the three constituents resulted in the formation of a new stereogenic centre at position C-2 of the acetamido group and provided diastereoselective reactions. The diastereomeric ratio ranged from 3:2 to 100:0. For the norbornane- and norbornene-based skeletons, completely diastereoselective reactions were observed in almost all cases.

The structure of **VIIIDbx**, as a representative example of the major isomers **VIIIDb** was determined by X-ray crystallography (Figure 4).





VIIIDb

Figure 4. Perspective view of VIIIDbx

4. SUMMARY

Regio- and stereospecific addition of CSI to (+)-3-carene **1** resulted in optically pure *β*-lactam **2**. Since the strongly constrained carene ring system was broken down during the conventional *β*-lactam ring-opening process, activation of the carboxamide bond seemed necessary. The ring-opening reactions of the *N*-Boc-protected azetidinone **3** under mild conditions resulted in the desired amino acid **7** and amino ester **6**, which was converted to the 1,3-amino alcohol. Both **6** and 1,3-amino alcohol **17** were convenient starting materials for further transformations to heterocycles. Amino ester was cyclized to 2-thioxo-4-pyrimidinone **13** and 2,4-pyrimidindione **15**, while the amino alcohol was converted to 2-phenylimino-1,3-oxazine **19**.

I also investigated the iodocyclization of cis-2-amino-3-cyclohexenecarboxylic acid derivatives. Ring opening of *β*-lactam **21**, followed by acylation, led to amide **23**, which was converted to iodooxazine **24** and iodooxazoline **25**. After a dehalogenation step, the *O,N*-heterocycles **24** and **25** were transformed to the desired hydroxy-substituted *β*-amino acids. The ring opening of deiodinated oxazine **26** gave 4-hydroxyamino acid **27**. When oxazoline **25** was dehalogenated, the ring-opened *N*-acetylamino ester **28** was observed, which was converted to 3-hydroxy-substituted analogue **30** via formation of a very stable amino lactone **29**.

Since the procedure described above was not highly effective, our attention turned to an iodolactonization protocol. The desired analogues, 3-hydroxy-substituted *β*-amino acids **30**, **35**, were also synthetized from *β*-lactam **21**. *N*-Boc protection of azetidinone **2**, followed by hydrolysis, resulted in *N*-Boc-amino acid **31**. The iodolactonization step afforded iodolactone **32** in good yield. After the deiodination step, opening of the *N*-Boc lactone **33** was attempted with different acidic reagents; variable mixtures of the desired hydroxyamino acid **30**, **35** and deprotected aminolactone **29**, **34** were observed, independently of the reaction conditions.

When our method was extended to the chiral compound (+)- and (-)-**38**, chiral 3-hydroxy-substituted *β*-amino acids were obtained. The hydroxyamino acid enantiomers (+)- and (-)-**35** were synthetized following a procedure similar to that used for the preparation of racemic amino acid **35** from racemic *N*-Boc amino acid **31**.

I investigated the applicabilities of alicyclic *β*-amino acids **I-VIII** as bifunctional compounds in the U-4C-3CR in water. Bi- and tricyclic *β*-lactams were synthetized in water by condensation of an aldehyde **A-D**, a *β*-amino acid **I-VIII** and an isonitrile **a**, **b** (Figure 2), their preparations being compared with those in MeOH. The diastereomeric ratio ranged from 3:2 to 100:0.

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